Immune system could be trained to spot drug-resistant cancers

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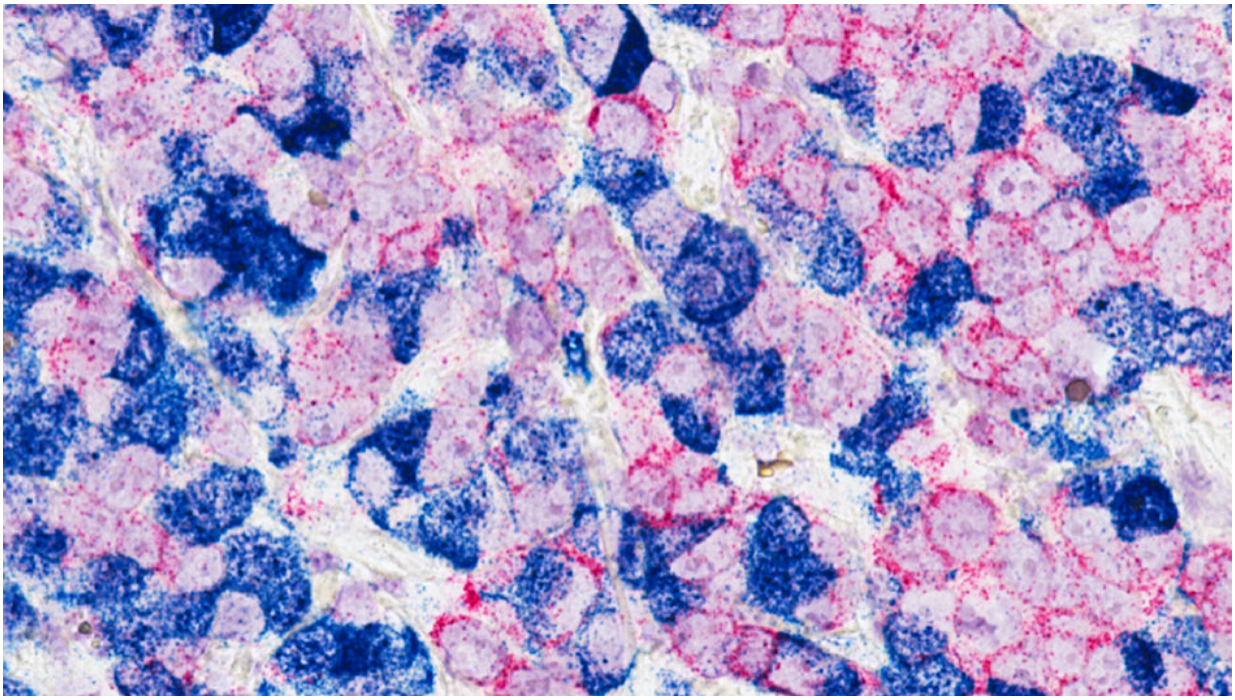

Breast cancer cells. Credit: Min Yu, via the National Cancer Institute

Aggressive cancers could be treated with immunotherapies that direct the immune system to kill cancer cells with specific drug resistance-causing mutations, a major new study suggests.

Drug resistance mutations which restore activity of the BRCA1 or BRCA2 genes as a way of avoiding the effects of drug treatment could

leave tumors vulnerable to the effects of immunotherapy, the research found.

Subtle differences in repaired genes

Scientists studied cancers that had evaded the effects of platinum chemotherapies and drugs called PARP inhibitors by repairing their BRCA genes—and found the new versions of the genes were subtly different from the same genes in healthy cells.

They believe the differences in these genes are big enough that it should be possible to train the body's immune system to spot and kill cancer cells with the repaired BRCA genes—opening up an exciting new way of treating cancers that are resistant to current drugs.

Scientists at The Institute of Cancer Research, London, compiled a database of more than 300 reported cases of mutations that rewire BRCA gene activity in order to become resistant to PARP inhibitors.

The study is published today in the major journal *Cancer Discovery*, and was funded by Cancer Research UK, Breast Cancer Now, and the Schottlander Research Charitable Trust.

Database characterizes molecular changes in drug resistant cancers

It aimed to characterize the molecular changes in cancers that have become resistant to platinum chemotherapy or PARP inhibitors—drugs which are now licensed for ovarian, breast, pancreatic and prostate cancers—and to open up new treatment strategies against them.

PARP inhibitors attack cancers which have mutations in BRCA genes or

various other genetic faults which leave them vulnerable to DNA damage.

However, cancers can sidestep the effects of PARP inhibitors or chemotherapy through genetic changes that switch the BRCA genes back on—known as reversion mutations.

The team from the CRUK Gene Function Laboratory and Breast Cancer Now Research Center at the Institute of Cancer Research (ICR) studied every reported incident of resistance associated with reversion mutations in BRCA-mutant cancers.

Could identify cancers at higher risk of developing resistance

The researchers found that some types of BRCA mutation were more likely than others to develop reversion mutations that restarted BRCA gene activity.

Detecting these mutations could pick out patients whose cancers might be expected to be at higher risk of developing resistance to treatment with PARP inhibitors or platinum chemotherapy.

Where reversion mutations occurred, the team found that the repaired BRCA genes created proteins which differed from normal cells. Computer models predicted that these would often be 'immunogenic' – meaning that the immune system would recognize them as foreign.

That raises the prospect that immunotherapies that take the brakes off the immune system could be effective against cancers with reversion mutations—pushing the body to generate a strong immune response against the repaired BRCA proteins. It may even be possible to generate

an immune response against the reverted BRCA proteins using a vaccine, if the reversion mutations can be predicted confidently.

Future reports of reversion mutations

The researchers have made their new database freely available for other scientists to use and collect future reports of these mutations, which could help identify further cancers that could be targeted with immunotherapies or other treatments.

Cancer's lethal ability to evolve resistance to drugs will be the focus of a pioneering drug discovery program in the ICR's new Center for Cancer Drug Discovery. The £75 million building will see around 300 evolutionary biologists and drug discovery scientists come together to understand and overcome the challenge of drug resistance, in order to turn cancer into a manageable disease that can be controlled in the long term and effectively cured.

In 2005, scientists at the Breast Cancer Now Research Center at the ICR found that PARP inhibitors kill cancer cells with BRCA gene mutations. Since then, the same scientists have been studying how resistance to these drugs develops.

By studying the DNA sequence of more than 300 patients across the world who had received a PARP inhibitor or platinum drug as part of their treatment, the scientists found how cancer cells rewire BRCA gene activity in order to become resistant to these drugs.

Crucial cancer research like this, aiming to find new treatments for patients, has been disrupted by the COVID-19 pandemic. The ICR, a charity and research institute, has launched a major fundraising appeal to kick-start its research and make up for the time lost to the coronavirus crisis.

Potential for an exciting new avenue of treatment

Study leader Professor Chris Lord, Deputy Head of Breast Cancer Research at The Institute of Cancer Research, London, said:

"Cancers that have repaired their BRCA mutations are difficult to treat, as their cells have recovered some of the properties of normal cells—in many ways this means that there are no obvious vulnerabilities to target. But we often noted that the way in which some cancer cells repair BRCA genes means that the proteins that they make are not completely normal, and could be recognized by the immune system as foreign, opening up ways to target and treat these cancers by using the immune system. We could use immunotherapy drugs like checkpoint inhibitors to harness the body's immune response, and direct it at reversion mutations. That has the potential to open up an exciting new avenue of treatment for patients with aggressive cancers that are resistant to the best available current drugs."

Professor Paul Workman, Chief Executive of The Institute of Cancer Research, London, said:

"Cancer evolution and drug resistance is the biggest challenge we face in research and treatment today. Studies like this are incredibly valuable in dissecting out how, why and when cancers can evolve resistance to current drugs. Excitingly, this research opens up the potential for a brand new approach to treatment that uses cancer's defenses against it, by targeting the very mutations which give the disease resistance to existing drug therapy."

Dr. Emily Armstrong, research information manager at Cancer Research UK, said:

"Genetic faults in the BRCA genes are involved in multiple cancers

including breast and ovarian cancers, so tackling drug resistance associated with these genes could change the lives of a huge number of people. This is only a computational prediction at the moment, but it will be very exciting to test in the lab whether the immune system can indeed tell the difference between the healthy proteins and the rewired ones produced by cancer cells, and effectively turn the tumors' resistance mechanism against them."

More information: Stephen J. Pettitt et al. Clinical BRCA1/2 reversion analysis identifies hotspot mutations and predicted neoantigens associated with therapy resistance, *Cancer Discovery* (2020). DOI: 10.1158/2159-8290.CD-19-1485

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